The normal maintenance downtime for STN will be extended on December 15. STN will be unavailable beginning Saturday, December 15, at 17:00 U.S. Eastern Standard Time until Sunday, December 16, at 01:00.

The normal schedule for STN maintenance downtime (22:00 to 01:00) will resume on December 22.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:32:22 ON 14 DEC 2007

=> file reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 08:32:33 ON 14 DEC 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 DEC 2007 HIGHEST RN 957969-84-5
DICTIONARY FILE UPDATES: 13 DEC 2007 HIGHEST RN 957969-84-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

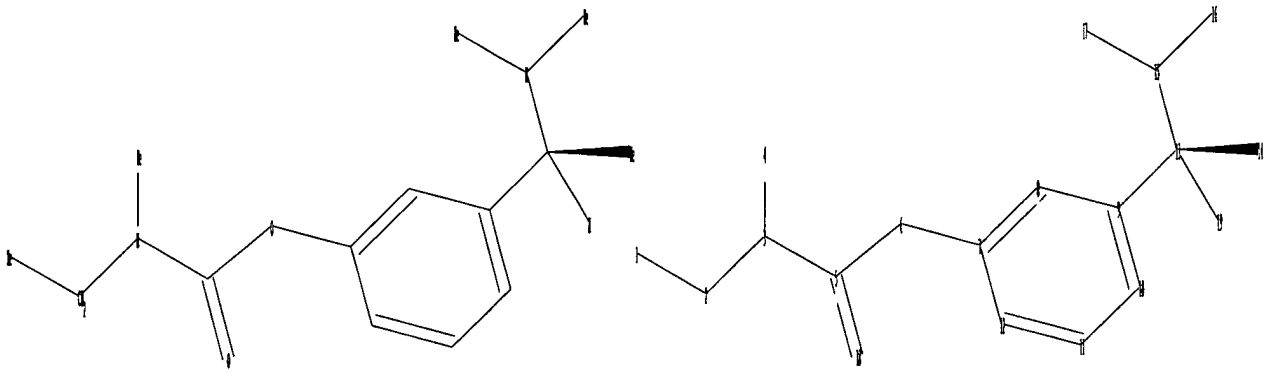
=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end

=> screen 964

L1 SCREEN CREATED

=>
Uploading C:\Program Files\Stnexp\Queries\10523927clm.str



chain nodes :
1 2 3 4 5 6 13 14 15 16 17 18 19
ring nodes :
7 8 9 10 11 12
chain bonds :
1-2 2-3 3-4 3-5 5-6 5-18 6-7 9-13 13-14 13-15 13-19 15-16 15-17
ring bonds :
7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
3-5 5-6 5-18 6-7 13-15
exact bonds :
1-2 2-3 3-4 9-13 13-14 13-19 15-16 15-17
normalized bonds :
7-8 7-12 8-9 9-10 10-11 11-12

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom

Stereo Bonds:

14-13 (Single Wedge).

Stereo Chiral Centers:

13 (Parity=Don't Care)

Stereo RSS Sets:

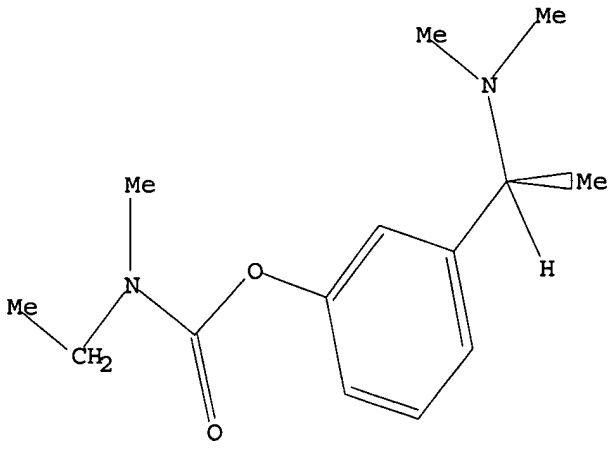
Type=Relative (Default). 1 Nodes= 13

L2 STRUCTURE UPLOADED

=> que L2 AND L1

L3 QUE L2 AND L1

=> d L2
L2 HAS NO ANSWERS
L2 STR




Structure attributes must be viewed using STN Express query preparation.

=> s L2 full
FULL SEARCH INITIATED 08:33:05 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 173 TO ITERATE

100.0% PROCESSED 173 ITERATIONS 18 ANSWERS
SEARCH TIME: 00.00.01

L4 18 SEA SSS FUL L2

=> file caplus

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 172.10 | 172.31 |

FILE 'CAPLUS' ENTERED AT 08:33:10 ON 14 DEC 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE COVERS 1907 - 14 Dec 2007 VOL 147 ISS 26
FILE LAST UPDATED: 13 Dec 2007 (20071213/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

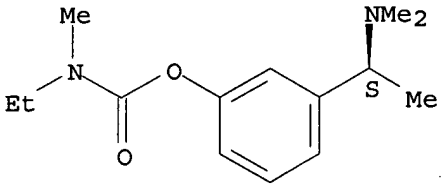
=> s L4
L5 603 L4

=> s hydrogen tartarate

```
       1032532 HYDROGEN
          6104 HYDROGENS
       1035925 HYDROGEN
                  (HYDROGEN OR HYDROGENS)
           656 TARTARATE
            33 TARTARATES
           685 TARTARATE
                  (TARTARATE OR TARTARATES)
L6           4 HYDROGEN TARTARATE
                  (HYDROGEN(W)TARTARATE)

=> s L5 (w) L6
L7           0 L5 (W) L6

=> s L5 and L6
L8           1 L5 AND L6

=> d L8 bib abs hitstr

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2005:503344  CAPLUS
DN   143:120709
TI   A validated chiral liquid chromatographic method for the enantiomeric
     separation of Rivastigmine hydrogen tartarate, a
     cholinesterase inhibitor
AU   Srinivasu, M. K.; Rao, B. Mallikarjuna; Reddy, B. Shyam Sundar; Kumar, P.
     Rajeneder; Chandrasekhar, K. B.; Mohakhud, Pradeep K.
CS   Analytical Research, Custom Pharmaceutical Services, Dr. Reddy's
     Laboratories, Hyderabad, 500049, India
SO   Journal of Pharmaceutical and Biomedical Analysis (2005), 38(2), 320-325
     CODEN: JPBADA; ISSN: 0731-7085
PB   Elsevier B.V.
DT   Journal
LA   English
AB   A new and accurate chiral liquid chromatog. method was developed for the
     enantiomeric resolution of Rivastigmine hydrogen tartrate,
     (-)S-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methylphenyl-carbamate hydrogen
     tartrate, a cholinesterase inhibitor in bulk drugs.  The enantiomers of
     Rivastigmine hydrogen tartrate were baseline resolved on a Chiralcel OD-H
     (250 mm + 4.6 mm, 5 μm) column using a mobile phase system containing
     hexane: isopropanol: trifluoroacetic acid (80:20:0.2, volume/volume/v).  The
     resolution between the enantiomers was not less than 4 and interestingly
     distomer was eluted prior to eutomer in the developed method.  The
     presence of trifluoroacetic acid in the mobile phase has played an
     important role in enhancing chromatog. efficiency and resolution between the
     enantiomers.  The developed method was extensively validated and proved to
     be robust.  The limit of detection and limit of quantification of
     (R)-enantiomer were found to be 500 and 1500 ng/mL, resp. for 10 μl
     injection volume  The percentage recovery of (R)-enantiomer was ranged from
     95.2 to 104.3 in bulk drug samples of Rivastigmine hydrogen tartrate.
     Rivastigmine hydrogen tartrate sample solution and mobile phase were found to
     be stable for at least 48 h.  The proposed method was found to be suitable
     and accurate for the quant. determination of (R)-enantiomer in bulk drugs.
     Chiralcel OJ-H column can also be used as an alternative for the above
     purpose.
IT   129101-54-8, Rivastigmine hydrogen tartrate 415973-05-6,
     (R)-Rivastigmine
     RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL
     (Biological study); USES (Uses)
        (enantiomeric separation of Rivastigmine hydrogen tartrate by HPLC)
RN   129101-54-8  CAPLUS
CN   Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
     ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1)  (CA INDEX NAME)

     CM   1
```

CRN 123441-03-2
CMF C14 H22 N2 O2

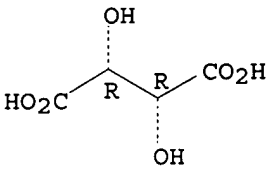
Absolute stereochemistry. Rotation (-).



CM 2

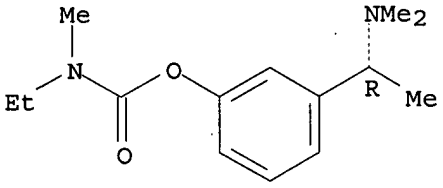
CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



RN 415973-05-6 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1R)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s process
2536922 PROCESS
1727961 PROCESSES
L9 3782401 PROCESS
(PROCESS OR PROCESSES)

=> s L9 and L5
L10 33 L9 AND L5

=> d L10 1-33 bib abs hitstr

L10 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:1116285 CAPLUS
DN 147:427355
TI Preparation of phenothiazine derivatives for treatment of tauopathy

IN Wischik, Claude Michel; Rickard, Janet Elizabeth; Harrington, Charles Robert; Horsley, David; Storey, John Mervyn David; Marshall, Colin; Sinclair, James Peter
PA Wista Laboratories Ltd., Singapore
SO PCT Int. Appl., 49pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007110630 | A1 | 20071004 | WO 2007-GB1107 | 20070328 |

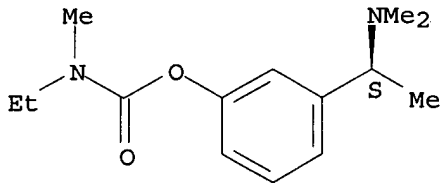
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2006-786699P P 20060329

AB This invention pertains to processes for the preparation of phenothiazine derivs. for the treatment of tauopathy, such as Alzheimer's disease. For example, 3-ethylaniline was reacted with Et iodide for N,N-diethyl-3-ethylaniline, which was treated with sodium nitrite in hydrochloric acid, and then with iron fillings in hydrochloric acid to obtain N4,N4,2-triethyl-1,4-benzenediamine dihydrochloride. The intermediate obtained above was treated with sodium sulfide, and then iron (III) chloride in water to give 3,7-bis(diethylamino)-1,9-diethyl-phenothiazin-5-ium chloride as a final product. The product obtained above showed inhibitory activity against tau protein aggregation in an in vitro assay with the concentration required to inhibit 50% of the tau-tau binding as 3.7 ± 0.5 μM.

IT 123441-03-2, Rivastigmine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of phenothiazine derivs. for treatment of tauopathy)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:993697 CAPLUS
DN 147:343798
TI Process for the preparation of carbamic acid 3-(aminoalkyl)phenyl esters
IN Wang, Zhi-Xian; Horne, Stephen E.; Murthy, K. S. Keshava

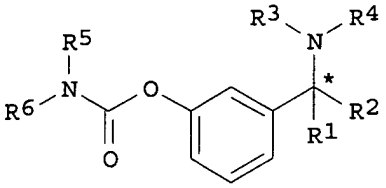
PA Can.
SO U.S. Pat. Appl. Publ., 6pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI US 2007207990 | A1 | 20070906 | US 2006-365596 | 20060302 |
| WO 2007098573 | A1 | 20070907 | WO 2007-CA253 | 20070228 |

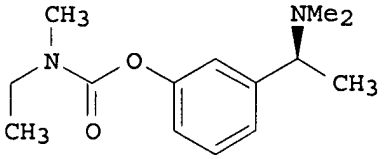
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2006-365596 A 20060302
OS CASREACT 147:343798; MARPAT 147:343798
GI




I



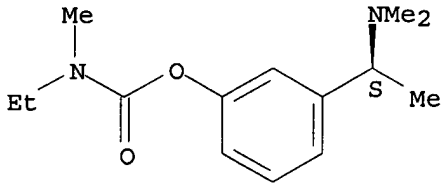

II

AB A process for the preparation of carbamic acid 3-(aminoalkyl)phenyl esters I [wherein R1, R2 independently = H or alkyl; R3, R4 independently = alkyl; R5, R6 independently = H or alkyl; R3 and R4, R5 and R6 together with the nitrogen to which they are attached form a cyclic three to eight membered ring, with or without a heteroatom like nitrogen or oxygen, resp.; the carbon center designated "*" can be racemic or enantiomerically enriched in the (R)- or (S)-configuration] and pharmaceutically acceptable acid addition salts thereof is disclosed. As an example, (S)-Rivastigime II was synthesized with >99.0% ee via treatment of the corresponding phenol with 1,1'-carbonyldiimidazole in acetonitrile followed by condensation with N-ethylmethylamine.

IT 123441-03-2P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carbamic acid (aminoalkyl)phenyl esters via carbamoylation of (aminoalkyl)phenols, carbonylating agents and amines)

RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




L10 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:986010 CAPLUS
DN 147:439300
TI Molecular pathology and pharmacogenomics in Alzheimer's disease: polygenic-related effects of multifactorial treatments on cognition, anxiety, and depression
AU Cacabelos, Ramon
CS EuroEspes Biomedical Research Center, Institute for CNS Disorders, Coruna, Spain
SO Methods and Findings in Experimental and Clinical Pharmacology (2007), 29(Suppl. A), 1-91
CODEN: MFEPDX; ISSN: 0379-0355
PB Prous Science
DT Journal; General Review
LA English
AB A review. Alzheimer's disease (AD) is a major problem of health in developed societies together with cardiovascular disorders and cancer. The lack of accurate diagnostic markers for early prediction and an effective therapy are the two most important problems to efficiently halt disease progression. The pharmacol. treatment in AD accounts for 10-20% of direct costs, and less than 20% of AD patients are moderate responders to conventional drugs (donepezil, rivastigmine, galantamine, memantine), with doubtful cost-effectiveness. The neuropathol. hallmark of AD (amyloid deposition in senile plaques, neurofibrillary tangle formation, and neuronal loss) are both the phenotypic expression of a pathogenic process in which more than 200 genes and their products are potentially involved. Drug metabolism, and the mechanisms underlying drug efficacy and safety, are also genetically regulated complex traits in which hundreds of genes cooperatively participate. Structural and functional genomics studies demonstrate that genomic factors, probably induced by environmental factors, cerebrovascular dysfunction, and epigenetic phenomena, might be responsible for AD pathogenic events leading to premature neuronal death. The AD population exhibits a higher genetic variation rate than the control population, with absolute and relative genetic variations of 40-60% and 0.85-1.89%, resp. AD patients also differ in their genomic architecture from patients with other forms of dementia. Functional genomics studies in AD reveal that age of onset, brain atrophy, cerebrovascular hemodynamics, brain bio-elec. activity, cognitive decline, apoptosis, immune function, lipid metabolism dyshomeostasis, and amyloid deposition are associated with AD-related genes. Pioneering pharmacogenomics studies also demonstrate that the therapeutic response in AD is genotype-specific, with APOE-4/4 carriers as the worst responders to conventional treatments. About 10-20% of Caucasians are carriers of defective CYP2D6 polymorphic variants that alter the metabolism and effects of AD drugs and many psychotropic agents currently administered to patients with dementia. There is a moderate accumulation of AD-related genetic variants of risk in CYP2D6 poor metabolizers and ultra-rapid metabolizers, which are the worst responders to conventional drugs. With diverse multifactorial therapies, combining different types of drugs and metabolic factors, it is partially possible to slowdown cognitive deterioration, improving non-cognitive symptoms, such as anxiety and depression, which currently aggravate cognition and increase the difficulties in disease management: however, the association of the APOE-4 allele with specific genetic variants of other genes (e.g., CYP2D6, ACE)

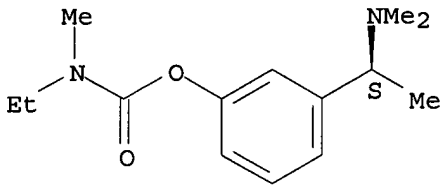
neg. modulate the therapeutic response to multifactorial treatments affecting cognition, mood and behavior. Pharmacogenetic and pharmacogenomic factors may account for 60-90% of drug variability in drug disposition and pharmacodynamics. The incorporation of pharmacogenetic/pharmacogenomic protocols to AD research and clin. practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(donepezil, rivastigmine, galantamine and memantine were used in patient with Alzheimer's disease)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 684 THERE ARE 684 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:919756 CAPLUS

DN 147:322710

TI Process for preparation of N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine

IN Tang, Zhaojun; Fu, Xiaoming

PA Hangzhou Shengmei Medicine Technology Development Co., Ltd., Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 12pp.
CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | CN 101016257 | A | 20070815 | CN 2007-10067343 | 20070214 |
| PRAI | CN 2007-10067343 | | 20070214 | | |

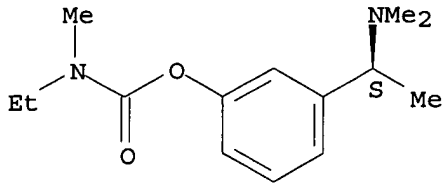
AB This invention pertains to a method for producing N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester. The compound is applied as intermediate of rivastigmine for treating Alzheimer's disease. The preparation method has the advantages of high product yield and quality, low cost, and simple operation.

IT 123441-03-2P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

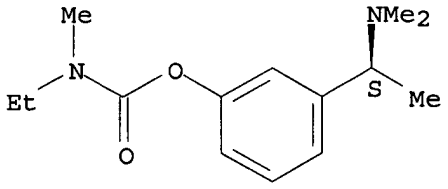



IT 129101-54-8P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine)
RN 129101-54-8 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

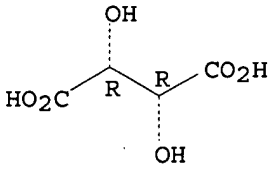
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.




L10 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:609363 CAPLUS
DN 147:39157
TI Transdermal therapeutic systems providing specific plasma concentrations of active ingredients, such as cholinesterase inhibitors
IN Gargiulo, Paul M.; Lane, Roger Michael; Wall, Bettina; Platt, Beatrix; Theobald, Frank
PA Novartis AG, Switz.; LTS Lohmann Therapie-Systeme AG
SO Can. Pat. Appl., 37pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | CA 2563110 | A1 | 20070601 | CA 2006-2563110 | 20061010 |
| | US 2007128263 | A1 | 20070607 | US 2006-539979 | 20061010 |
| | WO 2007064407 | A1 | 20070607 | WO 2006-US39557 | 20061010 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2005-741511P P 20051201

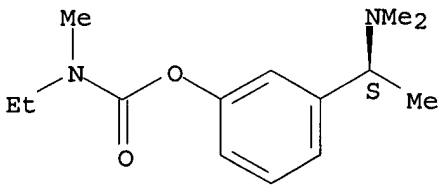
AB The present invention relates to a transdermal therapeutic system (TTS) with improved compliance, adhesion, tolerability and/or safety that provides specific plasma concns. of an active agent, e.g., a cholinesterase inhibitor. The TTS comprises (a) a backing layer, (b) a reservoir (matrix) layer containing one or more active ingredients and one or more polymers, and (c) a silicone adhesive layer containing a silicone polymer and a tackifier. The TTS comprises an addnl. detachable protective layer. A process of manufacturing and use of the TTS are also described. Thus, a bilayer TTS was produced comprising (i) a polymer matrix layer containing rivastigmine 30.0%, acrylic adhesive Durotak 387-2353 49.9%, acrylate polymer Plastold B 20.0%, and vitamin E 0.1%, and (ii) a silicone adhesive layer containing Bio-PSA Q7-4302 98.9%, silicone oil 1.0%, and vitamin E 0.1%. The saturation solubility of rivastigmine in the silicone adhesive was about 5% by weight The pharmacokinetic study in patients with Alzheimer's disease showed that the inter-patient variability of rivastigmine was lower after patch as compared to the oral administration. Also, improved pharmacol. properties of the patch compared with a capsule formulation were observed

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release transdermal therapeutic system comprising polymeric matrix and silicone adhesive)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




IT 129101-54-8, Rivastigmine hydrogen tartrate
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release transdermal therapeutic system comprising polymeric matrix and silicone adhesive)

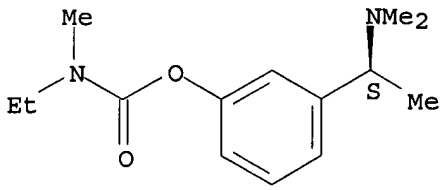
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

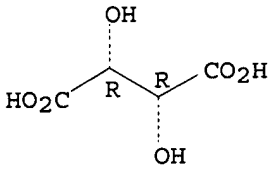
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



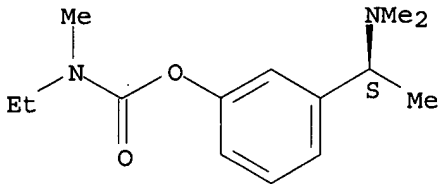

L10 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:545009 CAPLUS
DN 147:30831
TI Synthesis of rivastigmine
IN Chen, Weimin; Feng, Jin; Sun, Pinghua
PA Jinan University, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 7pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | CN 1962624 | A | 20070516 | CN 2006-10123473 | 20061110 |
| PRAI | CN 2006-10123473 | | 20061110 | | |

OS CASREACT 147:30831
AB The chemical name of rivastigmine is (S)-N-ethyl-3-[(1-dimethylamino)acrtyl]-N-methyl-carbamate Ph ester. The title method comprises the steps of: (1) performing a reaction of m-hydroxyacetophenone with N,N-dimethylformamide at a mol. ratio of 1:(4-800), 155-170°C and normal pressure for 5-24 h to obtain 3-[1-(dimethylamino)ethyl]phenol, and (2) esterifying with methylethylaminoformyl chloride at a mol. ratio of 1:1.05 to obtain rivastigmine. The method is environment-friendly, and has the advantages of simple process, convenient and safe operation, wide raw material resources, and little pollution.
IT 123441-03-2P, Rivastigmine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of rivastigmine)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl

ester (CA INDEX NAME)

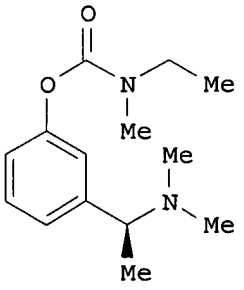
Absolute stereochemistry. Rotation (-).



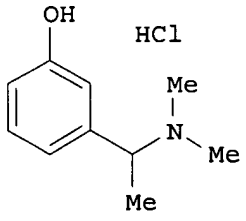
L10 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:397779 CAPLUS
DN 147:541597
TI Process for the preparation of rivastigmine
IN Parekh, Nayan Ratilal; Patil, Dhananjay Pandit
PA Torrent Pharmaceuticals Ltd., India
SO Indian Pat. Appl., 42pp.
CODEN: INXXBQ
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI IN 2004MU00682 | A | 20060616 | IN 2004-MU682 | 20040625 |
| PRAI IN 2004-MU682 | | 20040625 | | |

GI



I



II

AB The invention relates to a process for the preparation of the (2R,3R)-tartrate salt of rivastigmine (I), which is a carbamate-type reversible cholinesterase inhibitor. Rivastigmine is used for the treatment of the cognitive, functional, and behavioral symptoms of Alzheimer's disease. The process of the invention avoids the use of expensive and/or hazardous reagents such as sodium cyanoborohydride and sodium hydride, and provides a higher yield of the final product. The target compound may be prepared according to the process of the invention as shown by the following example. Reductive amination of 3-hydroxyacetophenone with dimethylamine in the presence of sodium borohydride and titanium(IV) isopropoxide gave amine II in 36% yield. The amine underwent carbamate formation with N-ethyl-N-methylcarbamoyl chloride in the presence of potassium hydroxide in DMSO to form racemic rivastigmine in 99% yield. Diastereomeric salt resolution of rivastigmine followed by liberation of the free base and salt formation with (R,R)-tartaric acid gave the tartrate salt of I in 6.5% overall yield.

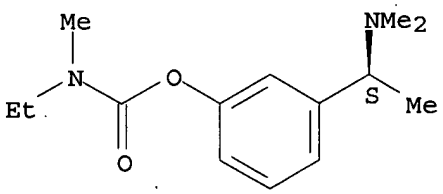
IT 399515-02-7P
RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(chiral intermediate; process for the preparation of rivastigmine)
RN 399515-02-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with 3-[(1S)-1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

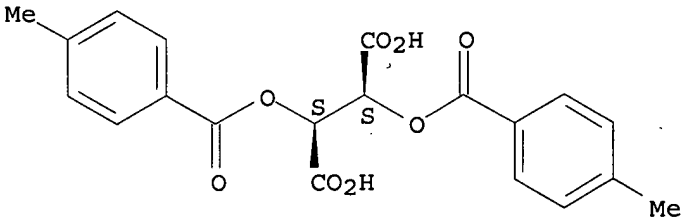
Absolute stereochemistry. Rotation (-).



CM 2

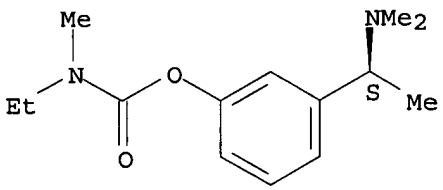
CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



IT 123441-03-2P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; process for the preparation of rivastigmine)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



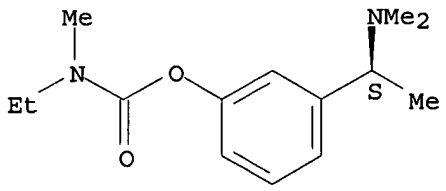
IT 129101-54-8P, Rivastigmine tartrate
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target compound; process for the preparation of rivastigmine)
RN 129101-54-8 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl

ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

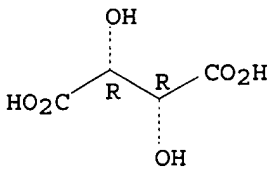
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.




L10 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:257897 CAPLUS
DN 146:295621
TI Process for preparation of rivastigmine and tartrate
IN Ma, Dawei; Pan, Qiangbiao; Pan, Song
PA Shanghai Aobo Bio-Pharmaceutical Technology Co., Ltd, Peop. Rep. China; Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences; Zhejiang Huahai Pharmaceutical Co., Ltd.
SO PCT Int. Appl., 27pp.
CODEN: PIXXD2
DT Patent
LA Chinese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2007025481 | A1 | 20070308 | WO 2006-CN2246 | 20060901 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| | RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | CN 1923801 | A | 20070307 | CN 2005-10029393 | 20050902 |
| PRAI | CN 2005-10029393 | A | 20050902 | | |

OS CASREACT 146:295621; MARPAT 146:295621

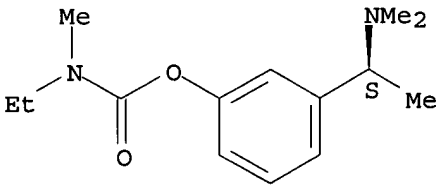
AB The present invention relates to a process for preparing N-ethyl-N-methyl-3-[(1S)-1-(dimethylamino)ethyl]phenyl carbamate (rivastigmine) and its tartrate, which comprises reacting 3-[(1S)-1-(dimethylamino)ethyl]phenol or salts with phosgene, diphosgene or triphosgene, followed by the addition of N-methylethanamine to give rivastigmine. The tartrate was obtained by reacting rivastigmine with L-(+)-tartaric acid. The process has the advantages of high yield and optical purity.

IT 123441-03-2P, Rivastigmine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of rivastigmine and tartrate)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




IT 129101-54-8P, Rivastigmine tartrate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of rivastigmine and tartrate)

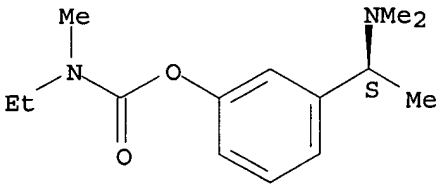
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

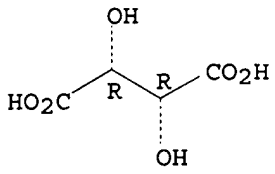
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.




RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

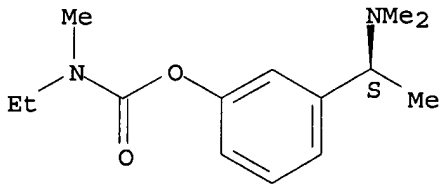
L10 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:257389 CAPLUS
DN 146:295628
TI Process for preparing enantiomerically pure rivastigmine
IN Jaweed, Mukarram Siddiqui Mohammed; Upadhye, Bhargav Krishnaji; Rai, Vikas Chandra; Zia, Hanfi
PA Wockhardt Limited, India
SO PCT Int. Appl., 16pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2007026373 | A2 | 20070308 | WO 2005-IN293 | 20050901 |
| WO 2007026373 | A3 | 20070712 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRAI WO 2005-IN293 20050901
OS CASREACT 146:295628; MARPAT 146:295628
AB An improved process for the preparation of enantiomerically pure rivastigmine, a selective acetylcholinesterase inhibitor, and its pharmaceutically acceptable salts is disclosed. Thus, 3-hydroxyacetophenone was treated with dimethylamine hydrochloride in presence of sodium cyanoborohydride to give an aminophenol. The aminophenol obtained was then treated with ethylmethylcarbamoyl chloride in presence of potassium tert-butoxide to obtain a carbamate. The carbamate was reacted di-p-toluoyl-D-tartaric acid in methanol to give a solid salt, which was recrystd. from methanol and basified with ammonia to give rivastigmine having > 99% enantiomeric purity.
IT 123441-03-2P, Rivastigmine 129101-54-8P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of enantiomerically pure rivastigmine and its salt from hydroxyacetophenone and carbamoyl halide)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

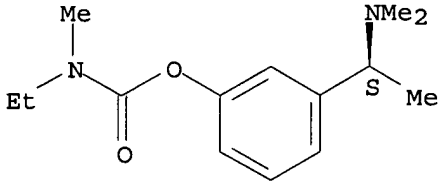



RN 129101-54-8 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

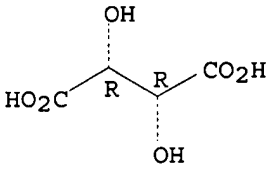
Absolute stereochemistry. Rotation (-).




CM 2

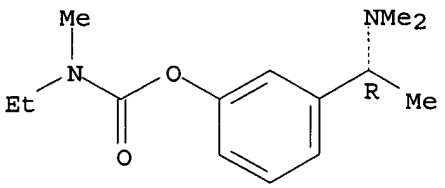
CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



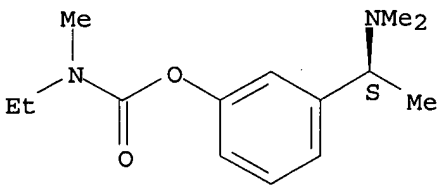

IT 415973-05-6P, (R)-Rivastigmine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of enantiomerically pure rivastigmine and its salt from hydroxyacetophenone and carbamoyl halide)
RN 415973-05-6 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1R)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry.



L10 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:225637 CAPLUS
DN 146:477753
TI Characterization of reversible and pseudo-irreversible acetylcholinesterase inhibitors by means of an immobilized enzyme reactor
AU Bartolini, Manuela; Cavrini, Vanni; Andrisano, Vincenza
CS Department of Pharmaceutical Sciences, University of Bologna, Bologna, 40126, Italy
SO Journal of Chromatography, A (2007), 1144(1), 102-110
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier B.V.
DT Journal
LA English
AB The aim of the present study was the application of a human AChE-CIM-IMER (enzyme reactor containing acetylcholinesterase immobilized on a monolithic disk) for the rapid evaluation of the thermodn. and kinetic consts., and the mechanism of action of new selected inhibitors. For this application, human recombinant AChE was covalently immobilized onto an ethylenediamine (EDA) monolithic Convective Interaction Media (CIM) disk and online studies were performed by inserting this IMER into a HPLC system. Short anal. time, absence of backpressure, low nonspecific matrix interactions and immediate recovery of enzyme activity were the best characteristics of this AChE-CIM-IMER. Mechanisms of action of selected reversible inhibitors (tacrine, donepezil, edrophonium, ambenonium) were evaluated by means of Lineweaver-Burk plot anal. Analyses were performed online by injecting increasing concns. of the tested inhibitor and substrate and by monitoring the product peak area. AChE-CIM-IMER kinetic parameters (Kappm and vappmax) were derived as well as inhibitory consts. (Kappi) of selected compds. Moreover, noteworthy results were obtained in the application of the AChE-CIM-IMER to the characterization of the carbamoylation and decarbamoylation steps in pseudo-irreversible binding of carbamate derivs. (physostigmine and rivastigmine). AChE-CIM-IMER appeared to be a valid tool to determine simultaneously the kinetic consts. in a reliable and fast mode. The obtained values were found in agreement with those obtained with the classical methods with the free enzyme. Furthermore, after inactivation by carbamates, activity could be fully recovered and the AChE-CIM-IMER could be reused for further studies. Results showed that the AChE-CIM-IMER is a valid tool not only for automated fast screening in the first phase of the drug discovery process but also for the finest characterization of the mode of action of new hit compds. with increased accuracy and reproducibility and with saving of time and materials.
IT 123441-03-2, Rivastigmine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of reversible and pseudo-irreversible acetylcholinesterase inhibitors by means of immobilized enzyme reactor)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:1210398 CAPLUS
DN 146:155046
TI Rivastigmine in Parkinson's disease dementia
AU Siddiqui, M. Asif A.; Wagstaff, Antona J.
CS Adis International Limited, Auckland, N. Z.
SO CNS Drugs (2006), 20(9), 739-747
CODEN: CNDREF; ISSN: 1172-7047
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Rivastigmine is a carbamate-type dual inhibitor of brain acetyl- and butyrylcholinesterases that has been evaluated in the symptomatic treatment of patients with mild to moderate dementia associated with idiopathic Parkinson's disease. Oral rivastigmine 3-12 mg/day for 24 wk was significantly more effective than placebo in ameliorating cognitive and functional decline, including attentional deficits, in patients with Parkinson's disease dementia in a randomized, double-blind trial. The beneficial effects of rivastigmine observed in the double-blind trial were generally maintained in a 24-wk extension of this study in which all patients received active treatment; placebo recipients who switched to rivastigmine also experienced improvements in their cognitive and functional symptoms at week 48. Rivastigmine appeared to be generally well tolerated, with the most common adverse events being mild to moderate in intensity and cholinergic in nature. Parkinsonian symptoms (mainly tremor) were more common in rivastigmine than placebo recipients. The hallmark of Parkinson's disease, the second most common neurodegenerative disorder, is motor system impairment causing resting tremor, bradykinesia, rigidity and postural instability. However, a combination of cognitive and neuropsychiatric symptoms is frequently found in these patients, and a progressive dementia syndrome develops in patients with longstanding disease, especially in elderly patients with severe disease. Dementia worsens the health-related quality of life of patients; it is associated with more rapid motor and functional decline, increased risk for institutionalization and increased mortality, as well as adding to caregiver distress. Patients with Parkinson's disease have an up to six-times higher risk of developing dementia than that in nondemented elderly patients without the disease. Approx. 28-44% of patients with Parkinson's disease experience dementia, with a cumulative prevalence of 78% reported over an 8-yr period in a longitudinal study using DSM-III revised diagnostic criteria. The presence of visual hallucinations or akinetic-dominant or mixed tremor/akinetic Parkinson's disease increases the risk of dementia 3-fold. The neuropathol. of Parkinson's disease dementia is likely a multifactorial process involving derangement of multiple populations of neurons in both the subcortical and cortical regions. A greater cholinergic deficit has been reported in Parkinson's disease dementia than in Alzheimer's disease; the extent of this deficit correlates with the severity of cognitive symptoms. Of the two cholinesterases hydrolyzing acetylcholine in the human brain, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), initial research has focused on the inhibition of AChE as cholinergic therapy of dementias. However, there is an increasing recognition of the role of BuChE in the normal and diseased brain. Current evidence indicates that, as AChE activity declines with the progressive loss of cortical neurons in Alzheimer's disease, BuChE levels increase and may take over the function to metabolize acetylcholine at the synapse. Furthermore, in dementia of Lewy bodies, the rate of cognitive decline has been shown to correlate with BuChE levels in the temporal cortex. Therefore, there may be at least a theor. advantage of a dual inhibitor of AChE and BuChE over a selective AChE inhibitor. Rivastigmine is a carbamate-type, dual inhibitor of AChE and BuChE that has been widely used as a cholinergic agent in the symptomatic treatment of Alzheimer's disease; the efficacy and tolerability of rivastigmine in this indication have been reviewed previously. This article focuses on the use of rivastigmine in dementia

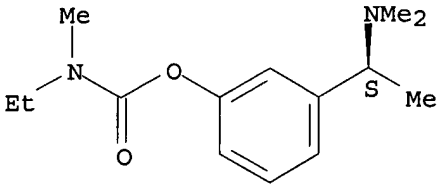
associated with Parkinson's disease.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of rivastigmine in treatment of patients with dementia associated with Parkinson's disease)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2006:533544 CAPLUS

DN 145:465467

TI Are cholinergic enhancers beneficial for memory in schizophrenia? An event-related potentials (ERPs) study of rivastigmine add-on therapy in a crossover trial

AU Guillem, Francois; Chouinard, Sylvie; Poulin, Julie; Godbout, Roger; Lalonde, Pierre; Melun, Pierre; Bentaleb, Lahcen Ait; Stip, Emmanuel

CS Hopital L-H Lafontaine, Centre de Recherche Fernand-Seguin, Montreal, QC, H1N 3V2, Can.

SO Progress in Neuro-Psychopharmacology & Biological Psychiatry (2006), 30(5), 934-945
CODEN: PNPPD7; ISSN: 0278-5846

PB Elsevier B.V.

DT Journal

LA English

AB Studies have reported beneficial effects of cholinergic enhancers, e.g., rivastigmine, on memory in schizophrenia but others have not. Possibly, these discrepancies are related to the lack of specificity of the tests used. This study investigated the effect of rivastigmine on memory in schizophrenia using event-related potentials (ERPs). Eighteen patients treated with atypical antipsychotic received rivastigmine adjuvant therapy in a randomized, crossover design. They were assessed at baseline (T1) and on two subsequent occasions (T2 and T3), where one half of the subjects were taken rivastigmine and the other half not. ERPs were recorded during a recognition memory task on each session. Behavioral and ERP data were analyzed using mixed ANOVA models first at T1 to detect potential group differences and for the trial (T1-T2) to determine the influence of rivastigmine, i.e., session+group interactions. The results showed no group difference at T1 except a trend for one group to be less efficient than the other on RT measures. When controlling for this difference the results on the trial data showed a trend for a benefit of rivastigmine on the RT memory effect. ERP anal. revealed that rivastigmine affects the amplitudes of two components elicited within 150-300 ms over posterior (reduced N2b) and frontal sites (enhanced P2a). It also enhances the magnitude of the memory (old/new) effect on two later components over posterior (N400) and frontal sites (F-N400). These results suggest that rivastigmine improves selective attention by enhancing interference inhibition processes (P2a) and lowering the reactivity to incoming stimulus (N2b). It also improves the integration of information with knowledge (N400) and with its context

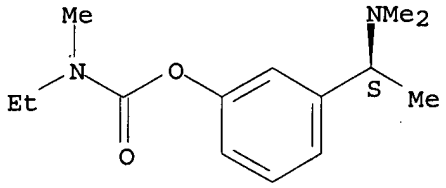
(F-N400). Generally, this study showed that the beneficial effect of rivastigmine on memory is not unitary but rather comes from its action at different time points within information processing cascade.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitor rivastigmine adjuvant therapy improved memory in schizophrenic patient)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2006:155049 CAPLUS

DN 145:76443

TI Short-term treatment with rivastigmine and plasma levels of Aβ peptides in Alzheimer's disease

AU Sobow, Tomasz; Kloszewska, Iwona

CS Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Lodz, 92-216, Pol.

SO Folia Neuropathologica (2005), 43(4), 340-344
CODEN: FONEEW; ISSN: 1641-4640

PB Termedia Publishing House

DT Journal

LA English

AB Deregulation of APP metabolism is considered to be a key pathogenic event in Alzheimer's disease. Data from cell cultures indicate that the secretion of Aβ1-42 might be inhibited by cholinesterase inhibitors, possibly via M1 receptors stimulation. Treatment with tacrine, a dual acetyl- and butyrylcholinesterase inhibitor, had no significant effect on mean plasma Aβ species concns. However, a correlation was observed between higher drug concns. and lower Aβ levels that might indicate an effect on APP metabolism with an increased α-cleavage. Aβ1-40 and Aβ1-42 levels were measured in the plasma of 28 AD subjects by means of a com. available ELISA before rivastigmine treatment and at week 2 after the first dose of the drug (3 mg/day) had been administered. Treatment with rivastigmine exhibited a significant effect on mean plasma concns. of Aβ1-42(mean difference 7.8 ± 8.4, t = -4.9, pmean difference 7.8 ± 8.4, t = -4.9, p < 0.001) with a neg. correlation with the patients age (Pearson's R = -0.40, p=0.035). No significant effect on plasma Aβ1-40 was observed The observed increase of mean levels of plasma Aβ1-42 after rivastigmine treatment might indicate an effect of the drug on Aβ metabolism, mobilization of Aβ1-42 from deposits in the affected brain areas and a consecutive Aβ1-42 brain-to-plasma efflux. The neg. correlation between Aβ1-42 plasma levels changes and age may be a sign of impairment of this process in the older patients. A large individual variation of the observed response, however, excludes drawing definite conclusions. Whether those subjects who respond to rivastigmine in terms of Aβ1-42 plasma levels changes also respond clin. needs to be established.

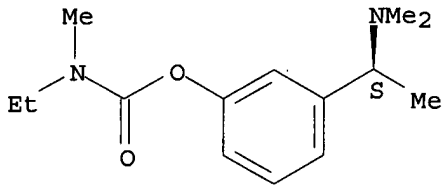
IT 123441-03-2, Rivastigmine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(short-term rivastigmine did not affect Aβ1-40, but significantly increased plasma Aβ1-42 level and decreased Aβ1-40/Aβ1-42 ratio which was correlated with age in Alzheimer's disease patient)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:1137923 CAPLUS

DN 143:399619

TI Rivastigmine is a potent inhibitor of acetyl- and butyrylcholinesterase in Alzheimer's plaques and tangles

AU Eskander, Mariam F.; Nagykery, Nicholas G.; Leung, Elaine Y.; Khelghati, Bahiyyih; Geula, Changiz

CS Laboratory for Neurodegenerative and Aging Research, Department of Medicine (Neuroscience), Harvard Medical School and Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA

SO Brain Research (2005), 1060(1-2), 144-152
CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier B.V.

DT Journal

LA English

AB Acetylcholinesterase and butyrylcholinesterase activities emerge in association with plaques and tangles in Alzheimer's disease. These pathol. cholinesterases, with altered properties, are suggested to participate in formation of plaques. The present experiment assessed the ability of rivastigmine, a clin. utilized agent that inhibits acetylcholinesterase and butyrylcholinesterase activities, to inhibit cholinesterases in plaques and tangles. Cortical sections from cases of Alzheimer's disease were processed using cholinesterase histochem. in the presence or absence of rivastigmine. Optical densities of stained sections were utilized as a measure of inhibition. The potency of rivastigmine was compared with those of other specific inhibitors. Optimum staining for cholinesterases in neurons and axons was obtained at pH 8.0. Cholinesterases in plaques, tangles and glia were stained best at pH 6.8. Butyrylcholinesterase-pos. plaques were more numerous than acetylcholinesterase-pos. plaques. Rivastigmine inhibited acetylcholinesterase in all pos. structures in a dose-dependent manner (10-6-10-4 M). However, even at the highest concentration, faint activity remained. In contrast, rivastigmine resulted in complete inhibition of butyrylcholinesterase in all structures at 10-5 M. Rivastigmine was equipotent to the specific acetylcholinesterase inhibitor BW284C51 and more potent than the butyrylcholinesterase inhibitors iso-OMPA and ethopropazine. In conclusion, rivastigmine is a potent inhibitor of acetylcholinesterase and a more potent inhibitor of butyrylcholinesterase in plaques and tangles. Unlike other cholinesterase inhibitors tested, rivastigmine inhibited cholinesterases in normal and pathol. structures with the same potency. Thus, at the therapeutic concns. used, rivastigmine is likely to result in inhibition of pathol.

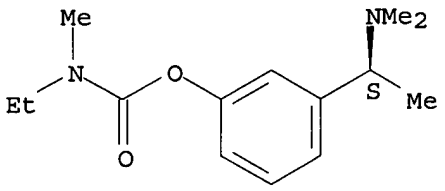
cholinesterases, with the potential of interfering with the disease process.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivastigmine is a potent inhibitor of acetyl- and butyrylcholinesterase in Alzheimer's plaques and tangles)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:1135771 CAPLUS

DN 143:416054

TI Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects

AU Wezenberg, E.; Verkes, R. J.; Sabbe, B. G. C.; Ruigt, G. S. F.; Hulstijn, W.

CS Department of Psychiatry (333), Radboud University Nijmegen Medical Center, Nijmegen, 6500, Neth.

SO Psychopharmacology (Berlin, Germany) (2005), 181(3), 582-594
CODEN: PSCHDL; ISSN: 0033-3158

PB Springer GmbH

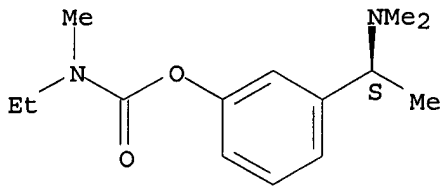
DT Journal

LA English

AB The central cholinergic system is implicated in cognitive functioning. The dysfunction of this system is expressed in many diseases like Alzheimer's disease, dementia of Lewy body, Parkinson's disease and vascular dementia. In recent animal studies, it was found that selective cholinergic modulation affects visuospatial processes even more than memory function. In the current study, the authors tried to replicate those findings. In order to investigate the acute effects of cholinergic drugs on memory and visuospatial functions, a selective anticholinergic drug, biperiden, was compared to a selective acetylcholinesterase-inhibiting drug, rivastigmine, in healthy elderly subjects. A double-blind, placebo-controlled, randomized, cross-over study was performed in 16 healthy, elderly volunteers (eight men, eight women; mean age 66.1, SD 4.46 years). All subjects received biperiden (2 mg), rivastigmine (3 mg) and placebo with an interval of 7 days between them. Testing took place 1 h after drug intake (which was around Tmax for both drugs). Subjects were presented with tests for episodic memory (word list and picture memory), working memory tasks (N-back, symbol recall) and motor learning (maze task, pursuit rotor). Visuospatial abilities were assessed by tests with high visual scanning components (tangled lines and Symbol Digit Substitution Test). Episodic memory was impaired by biperiden. Rivastigmine impaired recognition parts of the episodic memory performance. Working memory was nonsignificantly impaired by biperiden and not affected by rivastigmine. Motor learning as well as visuospatial processes were impaired by biperiden and improved by rivastigmine. These results implicate acetylcholine as a modulator not only of memory but also of visuospatial abilities.

IT 123441-03-2, Rivastigmine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1132655 CAPLUS
DN 143:393091
TI System and a method for producing layered oral dosage forms
IN Figueroa, Iddys D.; Ruiz, Orlando
PA USA
SO U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 2005233000 | A1 | 20051020 | US 2004-825870 | 20040416 |
| | WO 2005105038 | A2 | 20051110 | WO 2005-US11941 | 20050408 |
| | WO 2005105038 | A3 | 20070329 | | |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| | RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | EP 1758551 | A2 | 20070307 | EP 2005-734352 | 20050408 |
| | R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU | | | | |
| PRAI | US 2004-825870 | A | 20040416 | | |
| | WO 2005-US11941 | W | 20050408 | | |

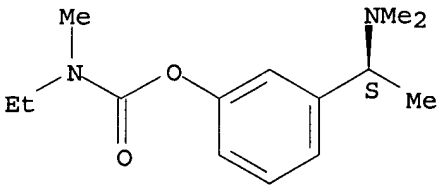
AB A method for producing an oral medication includes dispensing a structural material, the structural material including one of a polymer or a gelatin, curing the structural material, and dispensing a jettable pharmaceutical solution onto the cured structural material.
IT 129101-54-8, Rivastigmine tartrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(producing layered oral dosage forms)
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

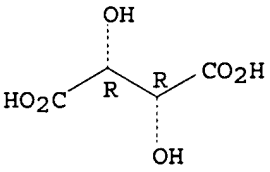
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.




L10 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1021603 CAPLUS
DN 143:311990
TI Combined pharmaceutical composition for the inhibition of the decline of cognitive functions
IN Levay, Gyoergy; Gacsalyi, Istvan; Harsing, Laszlo Gabor; Simig, Gyula
PA Egis Gyogyszergyar Rt., Hung.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2005087212 | A1 | 20050922 | WO 2004-HU22 | 20040312 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2004317129 | A1 | 20050922 | AU 2004-317129 | 20040312 |
| CA 2559493 | A1 | 20050922 | CA 2004-2559493 | 20040312 |
| EP 1727531 | A1 | 20061206 | EP 2004-720092 | 20040312 |

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, LT, LV, MK

| | | | | | |
|---|---|---|---|---|---|
| | CN 1925849 | A | 20070307 | CN 2004-80042405 | 20040312 |
| | BR 2004018634 | A | 20070529 | BR 2004-18634 | 20040312 |
| | JP 2007528892 | T | 20071018 | JP 2007-502417 | 20040312 |
| | IN 2006DN05448 | A | 20070803 | IN 2006-DN5448 | 20060919 |
| | NO 2006004644 | A | 20061211 | NO 2006-4644 | 20061012 |
| | BG 109701 | A | 20070630 | BG 2006-109701 | 20061012 |
| PRAI | WO 2004-HU22 | A | 20040312 | | |

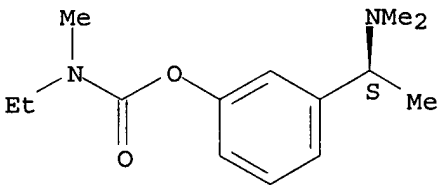
AB The invention relates to a combined pharmaceutical composition for the inhibition of the decline of cognitive functions comprising as A) component (1R,2S,4R)-(-)-2-[N,N-(dimethylaminoethoxy)]-2-phenyl-1,7,7-trimethylbicyclo]-2-phenyl-1.7.-trimethylbicyclo[2.2.1]heptane of the formula (I) or a pharmaceutically acceptable acid addition salt thereof and as B) component a nootropic, an inhibitor of the acetylcholinesterase enzyme and/or a further pharmaceutical active ingredient which exhibits a beneficial effect on the cognitive processes in admixt. with suitable inert pharmaceutical carriers and/or auxiliary agents. The combined pharmaceutical composition according to the present invention can be particularly used for the treatment of Alzheimer disease or other diseases showing similar symptoms, diseases accompanied by malfunctions of intellectual abilities (e.g. mental decline in schizophrenia), mental decline in elderly (dementias in elderly), Korsakoff syndrome, Huntington syndrome, Parkinson syndrome or mental decline produced by alcoholism.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined pharmaceutical composition for inhibition of decline of cognitive functions)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:983611 CAPLUS

DN 143:292527

TI Bioavailability and improved delivery of alkaline pharmaceutical drugs

IN Yu, Ruey J.; Van Scott, Eugene J.

PA USA

SO U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 792,273.
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 2005196418 | A1 | 20050908 | US 2005-50434 | 20050204 |
| | US 2004214215 | A1 | 20041028 | US 2004-792273 | 20040304 |
| | WO 2006084174 | A2 | 20060810 | WO 2006-US3917 | 20060206 |
| | WO 2006084174 | A3 | 20071004 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRAI US 2004-792273 A2 20040304
US 2003-452557P P 20030307
US 2005-50434 A 20050204

OS MARPAT 143:292527

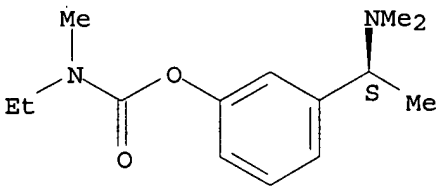
AB Embodiments of the invention relate to a composition, a process of making the composition, and to the use of the composition The compns. include a mol. complex formed between an alkaline pharmaceutical drug and at least one selected from a hydroxy acid, a polyhydroxy acid, a related acid, a lactone, or combinations thereof. The compns. provide improved bioavailability and improved delivery of the drug into the cutaneous tissues. For example, diphenhydramine hydrochloride 29 g (0.1 mol) was dissolved in water and 5 N sodium hydroxide generating diphenhydramine free base. Gluconolactone 18 g (0.1 mol) was added to form a mol. complex of 0.1 mol diphenhydramine free base with 0.1 mol gluconic acid/gluconolactone. The solution thus obtained was used for various forms of topical formulations including oil-in-water creams, lotions, gels and solns.

IT 123441-03-2, Rivastigmine
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(bioavailability and improved delivery of alkaline drugs by complexation with acids or lactones)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




L10 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:602193 CAPLUS

DN 143:399502

TI Effects of Rivastigmine on Sustained Attention in Schizophrenia: An fMRI Study

AU Aasen, Ingrid; Kumari, Veena; Sharma, Tonmoy

CS Department of Psychology, Institute of Psychiatry, London, UK

SO Journal of Clinical Psychopharmacology (2005), 25(4), 311-317
CODEN: JCPYDR; ISSN: 0271-0749

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB This study assessed the neural correlates of the effects of rivastigmine, a CNS-selective cholinesterase inhibitor, given as an add-on therapy to antipsychotics-treated patients with schizophrenia who displayed moderate

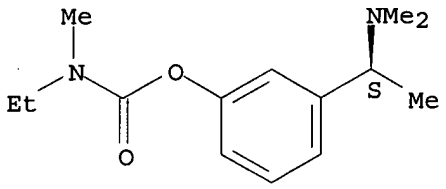
cognitive impairments, using functional magnetic resonance imaging (fMRI) during a sustained attention task. The study used a placebo-controlled, randomized, double-blind longitudinal design. Twenty patients stable on antipsychotics, 11 assigned to receive rivastigmine and 9 to receive placebo, underwent fMRI and clin. assessments at baseline and after 12 wk. The fMRI task used a periodic block design and involved 3 conditions: rest, detecting a nonzero number ("nonzero" condition), and detecting a specific number ("specific number" condition) among a series of 6-digit nos. Online data (via button presses) were acquired on both occasions. Behavioral results showed a trend (P = 0.075) for the rivastigmine-treated patients to have more correct responses and the placebo group to have fewer correct responses at 12 wk compared with baseline in the "nonzero" condition. There was also an increase in regional brain activity in the cerebellum in the rivastigmine group at 12 wk in both conditions, which was only partially explained by change in behavioral measures; no change was observed in the placebo group. Our results showed that rivastigmine treatment increased cerebellar activity and influenced attentional processes.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivastigmine treatment increased cerebellar activity and improved attention process in patient with schizophrenia)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:564631 CAPLUS

DN 143:97092

TI Stereoselective process for the preparation of tertiary amines attached to a secondary carbon center using a chiral transition metal transfer hydrogenation catalyst

IN Fieldhouse, Robin

PA Avecia Pharmaceuticals Limited, UK

SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

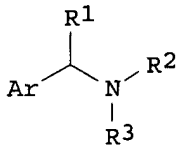
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2005058804 | A1 | 20050630 | WO 2004-GB5199 | 20041208 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, | | | | |

EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

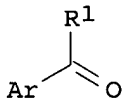
PRAI GB 2003-29284 A 20031218

OS CASREACT 143:97092; MARPAT 143:97092

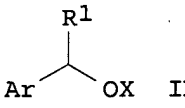
GI



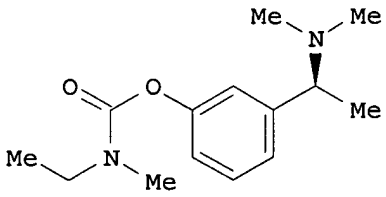
I



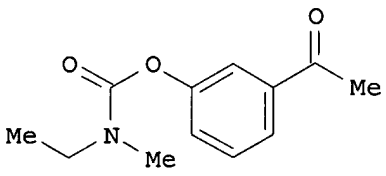
II



III



IV



V

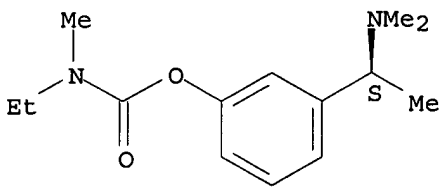
AB The invention provides a process for preparing tertiary amines I in three steps. In compds. I, Ar is (un)substituted hydrocarbon or (un)substituted heterocyclyl group comprising an aromatic moiety; and R1, R2, and R3 are independently selected from (un)substituted hydrocarbon and (un)substituted heterocyclyl. Ketone II is reduced to the corresponding secondary alc. by transfer hydrogenation. The alc. is converted to a leaving group to form compound III using the corresponding anhydride X-O-X (X = acetyl, trifluoroacetyl, methanesulfonyl, trifluoromethanesulfonyl, 4-toluenesulfonyl). Substitution of the leaving group with an amine (R2R3NH) then yields tertiary amine I. The invention also provides a stereoselective process for the preparation of I, where Ar and R1 are different. In this way, rivastigmine (IV) was prepared in 83% yield (3 steps) by way of an asym. transfer hydrogenation of V using a chiral rhodium catalyst. The preferred catalysts can be prepared in situ from bis[dichloro(pentamethylcyclopentadienyl)rhodium] and chiral N-camphorsulfonyl-1,2-diphenylethylene-1,2-diamine.

IT 123441-03-2P, Rivastigmine
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for the stereoselective preparation of tertiary amines attached to a secondary carbon center)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:561746 CAPLUS
DN 143:77963
TI Process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate
IN Gaitonde, Abhay; Mangle, Mangesh
PA Generics UK Limited, UK
SO Brit. UK Pat. Appl., 13 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2409453 | A | 20050629 | GB 2003-29970 | 20031224 |
| WO 2005061446 | A2 | 20050707 | WO 2004-GB50042 | 20041217 |
| WO 2005061446 | A3 | 20060105 | | |

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| EP 1697313 | A2 | 20060906 | EP 2004-806260 | 20041217 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS

| | | |
|---|---|---|
| PRAI GB 2003-29970 | A | 20031224 |
| WO 2004-GB50042 | W | 20041217 |

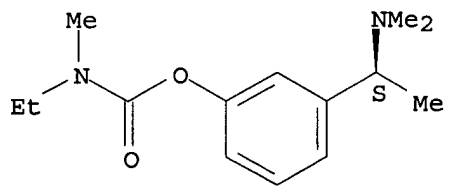
OS CASREACT 143:77963; MARPAT 143:77963

AB Rivastigmine hydrogentartrate is prepared from 3-hydroxyacetophenone in a process which has the advantage of avoiding the preparation of zwitterionic intermediates which are very water soluble and need to be isolated by concentration of aqueous solvent; this process is therefore suited to the industrial-scale manufacture of aminoalkylphenyl carbamates. The large amts. of sulfated ash residues left in the product when prepared by prior-art processes and the use of pyrophoric and reagents such as sodium hydride may be avoided by using the title method.

IT 123441-03-2P, Rivastigmine 129101-54-8P, Rivastigmine hydrogentartrate
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate)

RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

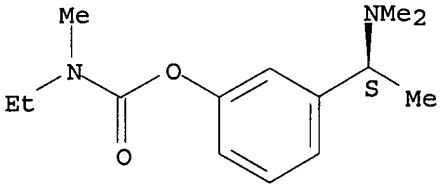


RN 129101-54-8 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

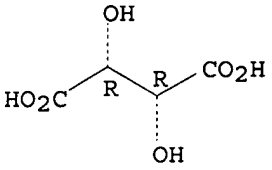
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.




RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1063811 CAPLUS
DN 142:373547
TI Process for preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts
IN Zhou, Ning; Xu, Xingxiang; Zhou, Zhishan
PA Sanwei Pharmaceutical Co., Ltd., Shanghai, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI CN 1486973 | A | 20040407 | CN 2003-141995 | 20030731 |
| PRAI CN 2003-141995 | | 20030731 | | |

OS CASREACT 142:373547
AB This invention pertains to a method for producing 3-[(1S)-1-(Dimethylamino)ethyl]phenyl N-ethyl-N- methylcarbamate and its salts by esterifying (S)-3-(1-dimethylaminoethyl)phenol with N-ethyl-N-methylcarbamoyl chloride in organic solvent (such as toluene, xylene, chlorobenzene, Et ether, THF, etc.) in the presence of a base (such as NaH, NaOH, triethylamine, etc.) at (-20)-70 °C, and adding an acid in alc. (ether, or Et acetate) solvent. The synthetic N-ethyl-N-methylcarbamate salts may be used for treating senile dementia

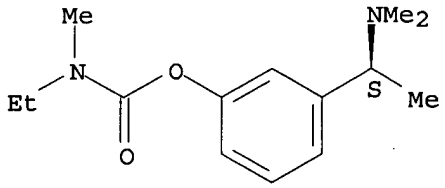
(no data).

IT 123441-03-2P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




IT 129101-54-8P 727418-36-2P 849466-24-6P
849466-25-7P 849466-28-0P 849466-31-5P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts)

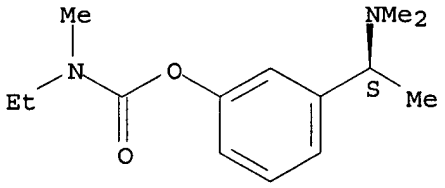
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

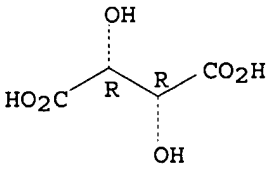
Absolute stereochemistry. Rotation (-).




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

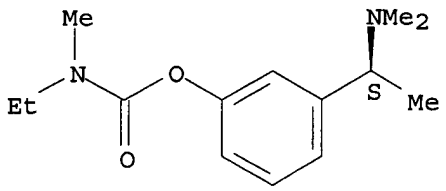



RN 727418-36-2 CAPLUS

CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester,

monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



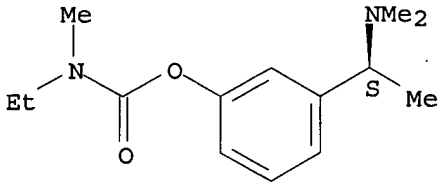

● HCl

RN 849466-24-6 CAPLUS
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

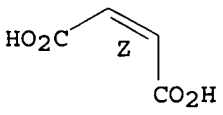
Absolute stereochemistry. Rotation (-).




CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.

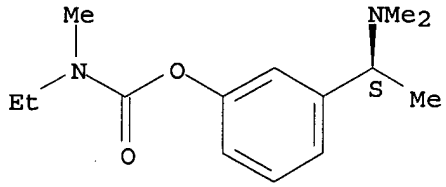



RN 849466-25-7 CAPLUS
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

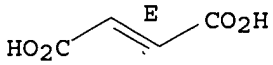
Absolute stereochemistry. Rotation (-).



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

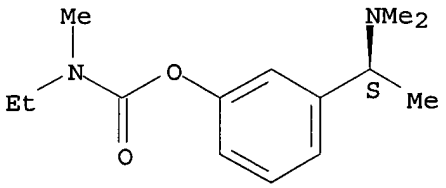


RN 849466-28-0 CAPLUS
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

CM 1

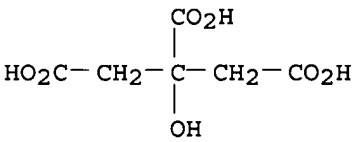
CRN 123441-03-2
CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).



CM 2

CRN 77-92-9
CMF C6 H8 O7

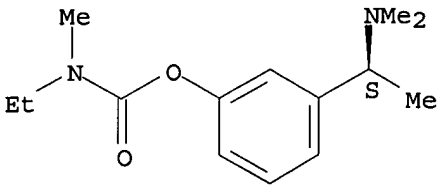


RN 849466-31-5 CAPLUS
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

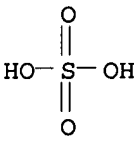
CRN 123441-03-2
CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).




CM 2

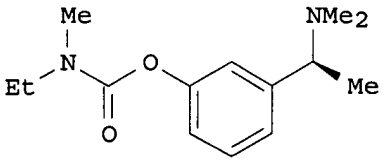
CRN 7664-93-9
CMF H2 O4 S



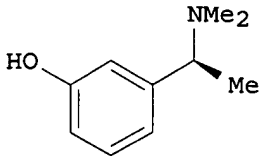

L10 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:622247 CAPLUS
DN 142:6315
TI Process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate (rivastigmine)
IN Stepankova, Hana; Hajicek, Josef; Simek, Stanislav
PA Leciva, A. S., Czech Rep.
SO Czech Rep., 12 pp.
CODEN: CZXXED
DT Patent
LA Czech
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | CZ 293014 | B6 | 20040114 | CZ 2002-3555 | 20021024 |
| | WO 2004037771 | A1 | 20040506 | WO 2003-CZ58 | 20031021 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | AU 2003277795 | A1 | 20040513 | AU 2003-277795 | 20031021 |
| | EP 1556338 | A1 | 20050727 | EP 2003-769173 | 20031021 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| | US 2006122417 | A1 | 20060608 | US 2005-523927 | 20050207 |
| PRAI | CZ 2002-3555 | A | 20021024 | | |
| | WO 2003-CZ58 | W | 20031021 | | |

GI



I



II

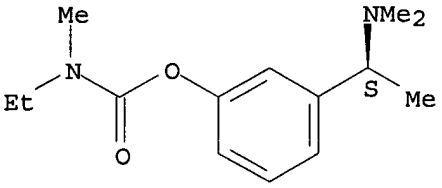
AB The invention relates to the process of preparing the title compound (S)-I or its tartrate salt which comprises (a) reacting (S)-II (preparation given starting from 3-methoxyacetophenone) with EtN(Me)COX [wherein X = a leaving group] to provide (S)-I, and (b) treating (S)-I with tartaric acid to afford (S)-I.tartrate.

IT 123441-03-2P, Rivastigmine 129101-54-8P, Rivastigmine tartrate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate (rivastigmine))

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



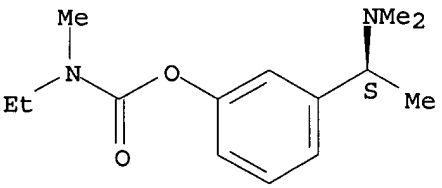
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

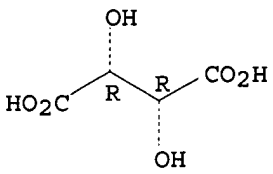
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

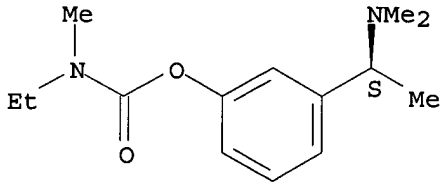


IT 399515-02-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate (rivastigmine))
RN 399515-02-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with 3-[(1S)-1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

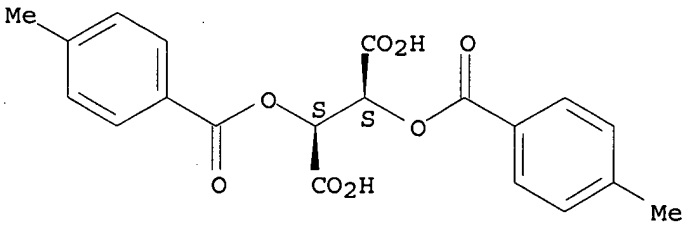
Absolute stereochemistry. Rotation (-).



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



L10 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:476369 CAPLUS
DN 141:405520
TI Acetylcholinesterase and its inhibition in Alzheimer disease
AU Lane, Roger M.; Kivipelto, Miia; Greig, Nigel H.
CS Novartis Neuroscience, Novartis Pharmaceuticls Corp, Pfizer Inc., East Hanover, NJ, USA
SO Clinical Neuropharmacology (2004), 27(3), 141-149
CODEN: CLNEDB; ISSN: 0362-5664
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English

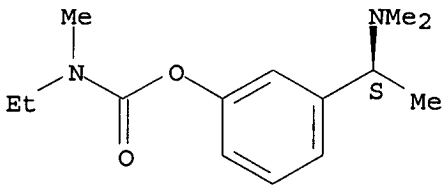
AB A review. Until recently, the only established function of acetylcholinesterase (AChE) was the termination of cholinergic neurotransmission. Therefore, the use of AChE inhibitors to treat symptoms caused by cholinergic imbalances in Alzheimer disease (AD) represented a rational approach. However, it is now clear that AChE and the cholinergic system may have broader effects in AD. Of particular interest may be signal transduction pathways mediated through cholinergic receptors that promote nonamyloidogenic amyloid precursor protein processing and decrease tau phosphorylation, and the role of AChE in the aggregation of β-amyloid (Aβ) peptide. In addition, the neuronal and nonneuronal cholinergic systems have important roles in the modulation of regional cerebral blood flow. These findings may modify the overly simplistic cholinergic hypothesis in AD that is limited to symptomatic treatment and ignores the potential of cholinergic therapies as disease-modifying agents. Chronic increases in AChE activity may exacerbate neurodegenerative processes, make clin. relevant levels of AChE inhibition more difficult to achieve, and cause the therapeutic value of cholinesterase inhibitors (ChE-Is) to be limited and temporary. Rapidly reversible ChE-Is appear to increase AChE activity over the longer term whereas, remarkably, irreversible or very slowly reversible ChE-Is do not seem to have this effect. If such differences between ChE-Is are shown to have clin. correlates, this may prompt reconsideration of the rationale and expectations of some agents in the long-term management of AD.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ChE-Is, donepezil, galantamine and tacrine induced marked elevations of AChE level showing adverse consequences in long term treatment but rivastigmine could not elevate AChE target enzyme level in brain of AD)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:64842 CAPLUS
DN 140:86958
TI Acetylcholinesterase inhibition in Alzheimer's disease
AU Ibach, Bernd; Haen, Ekkehard
CS Memory Disorders Clinic, Gerontopsychiatric and Clinical Pharmacology Research Unit, Department of Psychiatry, University of Regensburg, Regensburg, Germany
SO Current Pharmaceutical Design (2004), 10(3), 231-251
CODEN: CPDEFP; ISSN: 1381-6128
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Alzheimer's disease (AD) is the most common cause for dementia in our aging population, which leads to a slowly progressive, irretrievable ruination of mental function. The destructive, primarily degenerative condition is neuropathol. characterized by the formation of

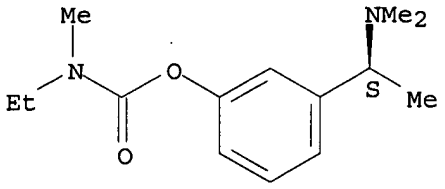
amyloid plaques, neurofibrillary tangles and loss of neurons and synapses as well. Research during the past twenty years revealed early in the disease course a degeneration of cholinergic nuclei localized in the basal forebrain. Impairment of this cholinergic system, which projects into large areas of the limbic system and the neocortex is followed by disturbance of attentional processes and cognitive decline. The link between the cholinergic dysfunction and cognitive impairment has focused large scientific efforts to understand the neurobiol. of cognition and to develop therapeutic tools for the fight against Alzheimer's disease. Acetylcholinesterase inhibitors are currently the best established treatment for this devastating disease. This review describes historical aspects and the vast range of use of cholinesterase inhibitors in traditional societies and industrial nations. Second, the rational basis will be outlined for their development as medication, the so-called cholinergic hypotheses of AD. Third, acetylcholinesterase inhibitors currently available for the treatment of AD will be reviewed. This includes donepezil, galanthamine and rivastigmine. Tacrine, the first acetylcholinesterase inhibitor who became available in 1993 as a treatment for AD, does not play an essential role anymore besides his historical value, because of its hepatotoxicity. Although acetylcholinesterase inhibitors are no cure, these drugs can delay the progress of mental deterioration, reduce neuropsychiatric symptoms and therefore represent a rational therapeutic approach to the treatment of Alzheimer's Disease.

IT 123441-03-2, Rivastigmine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitors for treatment of Alzheimer's disease)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 135 THERE ARE 135 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:972013 CAPLUS
DN 140:27668
TI A process for the preparation of phenyl carbamates
IN Thennati, Rajamannar
PA Sun Pharmaceutical Industries Limited, India; Patel, Hetalkumar Virendrabhai
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

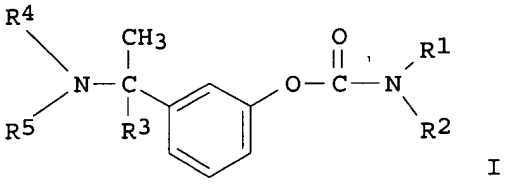
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2003101917 | A2 | 20031211 | WO 2003-IN210 | 20030602 |
| WO 2003101917 | A3 | 20040812 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| | IN 2002MU00484 | A | 20040228 | IN 2002-MU484 | 20020531 |
| | IN 2003MU00166 | A | 20050204 | IN 2003-MU166 | 20030206 |
| | AU 2003263574 | A1 | 20031219 | AU 2003-263574 | 20030602 |
| | US 2006293518 | A1 | 20061228 | US 2006-516104 | 20060807 |
| PRAI | IN 2002-MU484 | A | 20020531 | | |
| | IN 2003-MU166 | A | 20030206 | | |
| | WO 2003-IN210 | W | 20030602 | | |

OS CASREACT 140:27668; MARPAT 140:27668
GI



I

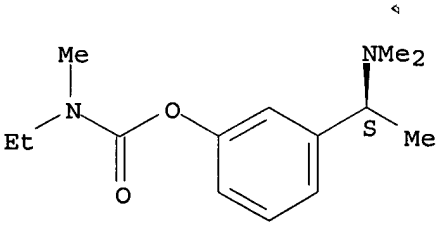
AB Phenylcarbamates [I; R1 = H, (un)branched lower (cyclo)alkyl, cyclohexyl, allyl, propargyl, benzyl; R2 = H, Me, Et, propyl; NR1R2 = three-to-eight-membered ring with or without a hetero atom like nitrogen or oxygen; R3 =H, lower alkyl; R4, R5 = lower alkyl; e.g., racemic rivastigmine] are prepared in high yield and selectivity by the reaction of the corresponding I phenol [e.g., 3-[(1-dimethylamino)ethyl]phenol] with a 4-nitrophenylcarbamate 4-O2NC6H4O2CN(R1)R2 (e.g., 4-nitrophenyl N-ethyl-N-methylcarbamate) in the presence of a base (e.g., potassium carbonate).

IT 123441-03-2P, Rivastigmine
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of Ph carbamates)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L10 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:847386 CAPLUS

DN 140:59356

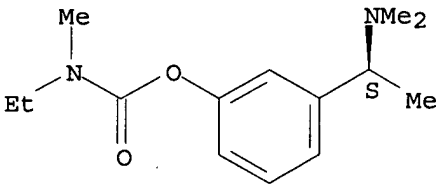
TI Asymmetric, Catalytic Synthesis of α-Chiral Amines Using a Novel Bis(phosphine) Monoxide Chiral Ligand

AU Boezio, Alessandro A.; Pytkowicz, Julien; Cote, Alexandre; Charette, Andre B.

CS Departement de Chimie, Universite de Montreal, Montreal, QC, H3C 3J7, Can.

SO Journal of the American Chemical Society (2003), 125(47), 14260-14261
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 140:59356
AB It was shown that (R,R)-Me-DuPhos monoxide [BozPHOS; (2R,2'R,5R,5'R)-1,1'-(1,2-phenylene)bis[2,5-dimethylphospholane] 1-oxide] is a very effective ligand in the copper-catalyzed addition of dialkylzinc to N-phosphinoylimines providing access to α-chiral amines. The new ligand is particularly effective for the addition of the lesser reactive dimethylzinc. The major advantages of this process are high yields, broad substrate scope, and high enantioselectivities with low catalyst loading (3 mol %). New compds. thus prepared included N-[(1S)-1-(2-methoxyphenyl)propyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(2-chlorophenyl)propyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(2-methylphenyl)propyl]-P,P-diphenylphosphinic amide,N-[(1S)-1-(3-methylphenyl)ethyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-phenylpentyl]-P,P-diphenylphosphinic amide, N-[(1S)-2-methyl-1-phenylpropyl]-P,P-diphenylphosphinic amide.
IT 123441-03-2P, (Ethyl)(methyl)carbamic acid 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester
RL: SPN (Synthetic preparation); PREP (Preparation)
(rivastigmine; asym., catalytic synthesis of chiral amines via reduction of diphenyl(phenylmethylene)phosphinic amides using (phenylene)bis[dimethylphospholane] oxide as ligand)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:353645 CAPLUS
DN 140:61086
TI Pharmaceuticals as antifoulants: concept and principles
AU Rittschof, Dan; Lai, Chien-Houng; Kok, Lai-Mun; Teo, Serena Lay-Ming
CS Duke University Marine Laboratory, Nicholas School of the Environment, Beaufort, NC, 28516-9721, USA
SO Biofouling (2003), 19(Suppl.), 207-212
CODEN: BFOUEC; ISSN: 0892-7014
PB Taylor & Francis Ltd.
DT Journal
LA English
AB The hypothesis that pharmaceuticals, with their known syntheses, chemical properties and primary mechanism of action would be an efficient source of new antifouling agents compatible with existing antifouling coating technol. was tested. Twenty-three compds. at concns. from 5 μg ml-1 to 40 ng ml-1 were tested for toxicity and inhibition of settlement of barnacle larvae. The compds. had a wide range of solubility in water and covered nine primary mechanisms of action in vertebrates. The upper level of potency was chosen because compds. that are highly potent have greater practical potential. The goal was to find compds. with high inhibition of settlement and low toxicity. Of the 23 compds. tested, 22 had significant

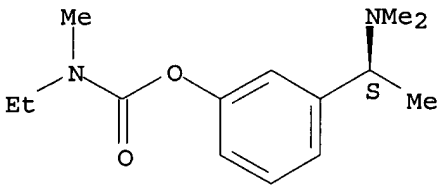
effects on barnacle larvae. The variety of chemical structures and their variation in water solubility support the hypothesis that pharmaceuticals that are compatible with existing coatings technol. should be considered as antifouling agents. Moreover, factors such as coating compatibility and environmental fate should be addressed early in the development process.

IT 123441-03-2, Exelon
RL: PAC (Pharmacological activity); PRP (Properties); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(evaluation of pharmaceuticals as potential antifoulants in marine coatings)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2002:895868 CAPLUS

DN 139:143316

TI ADME evaluation 2. A computer model for the prediction of intestinal absorption in humans

AU Klopman, Gilles; Stefan, Liliana R.; Saiakhov, Roustem D.

CS Department of Chemistry, Case Western Reserve University, Cleveland, OH, 44106, USA

SO European Journal of Pharmaceutical Sciences (2002), 17(4-5), 253-263
CODEN: EPSCED; ISSN: 0928-0987

PB Elsevier Science Ltd.

DT Journal

LA English

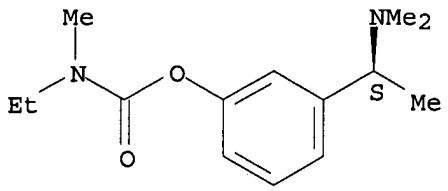
AB Purpose: To develop a computational method to rapidly evaluate human intestinal absorption, one of the drug properties included in the term ADME (Absorption, Distribution, Metabolism, Excretion). Poor ADME properties are the most important reason for drug failure in clin. development. Methods: The model developed is based on a modified contribution group method in which the basic parameters are structural descriptors identified by the case program, together with the number of hydrogen bond donors. Results: The human intestinal absorption model is a quant. structure-activity relationship (QSAR) that includes 37 structural descriptors derived from the chemical structures of a data set containing 417 drugs. The model was able to predict the percentage of drug absorbed from the gastrointestinal tract with an r2 of 0.79 and a standard deviation of 12.32% of the compds. from the training set. The standard deviation for an external test set (50 drugs) was 12.34%. Conclusions: The availability of reliable and fast models like the one we propose here to predict ADME/Tox properties could help speed up the process of finding compds. with improved properties, ultimately making the entire drug discovery process shorter and more cost efficient.

IT 123441-03-2, Rivastigmine
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(computer model for prediction of intestinal absorption in humans)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:645765 CAPLUS
DN 137:194868
TI Pharmacologic treatments of dementia
AU Bonner, Lauren T.; Peskind, Elaine R.
CS Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, 98108, USA
SO Medical Clinics of North America (2002), 86(3), 657-674
CODEN: MCNAA9; ISSN: 0025-7125
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A review. Alzheimer's disease (AD) and other forms of dementia are estimated to affect millions worldwide. Because ests. of the incidence and prevalence of dementia are criteria dependent, the true number of people affected by dementia in the United States is unknown. Is it estimated that AD, the most common cause of dementia, accounts for nearly 70% of dementias. There is still debate about the second and third most common forms of dementia. Recent neuropathol. studies have demonstrated that dementia with Lewy bodies (DLB) may be the second most common cause of dementia, accounting for 15-25% of dementia cases. Other sources consider vascular/multi-infarct dementia (VaD) to be the second most common cause of dementia. Because AD and other forms of dementia are diseases of the aged, prevalence rates should increase as our population continues to age. AD is estimated to affect 4 million Americans. Currently, approx. 5% of Americans aged 65 yr and older suffer from AD, with an estimated 30-50% of Americans aged 85 yr and older suffering from the disorder. By the year 2050, the number of Americans suffering from AD is estimated to rise to 14 million. AD is characterized by a gradual insidious onset of memory loss, global cognitive deterioration, and functional deterioration. Short-term memory is affected early in the course of the illness, reflecting early involvement of the hippocampus and medial temporal lobes. Visuospatial deficits and executive dysfunction also appear early in the illness. Gradually, as the disease process advances, all cognitive functions are impaired. The duration of the illness is 5 to 10 yr, with pneumonia or sepsis as the usual cause of death. The typical findings on neuropathol. examination include hippocampal and neocortical neuritic plaques, neurofibrillary tangles, and neuronal loss. Although there is no cure for AD, two pharmacol. treatment options can provide symptomatic improvement in cognitive and functional deterioration:cholinesterase inhibitors and vitamin E. Cholinesterase inhibitors, which exert their effects by increasing the availability of intrasynaptic acetylcholine, have been demonstrated to be more effective than placebo in the treatment of the cognitive deficits of AD. The antioxidant vitamin E (α-tocopherol) slows functional deterioration in AD. In this article, we review data supporting the use of cholinesterase inhibitors and vitamin E in the treatment of AD and related dementias and present recommendations for incorporating their use into clin. practice. Unless otherwise specified,

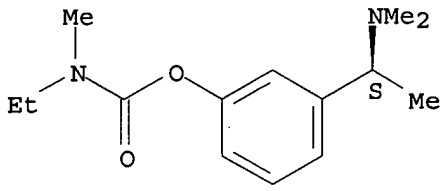
when specific effect sizes are described, the efficacy data presented were derived from anal. of observed cases.

IT 123441-03-2, Rivastigmine
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. treatments of dementia patients)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2000:899243 CAPLUS

DN 135:86295

TI RBC cholinesterase inhibition: A useful surrogate marker for cholinesterase inhibitor activity in alzheimer disease therapy?

AU Sramek, John J.; Cutler, Neal R.

CS California Clinical Trials, Beverly Hills, CA, 90211, USA

SO Alzheimer Disease and Associated Disorders (2000), 14(4), 216-227
CODEN: ADADE2; ISSN: 0893-0341

PB Lippincott Williams & Wilkins

DT Journal; General Review

LA English

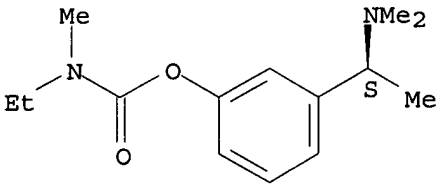
AB A review with 91 refs. Red blood cell (RBC) acetylcholinesterase (AChE) inhibition has been used as a peripheral surrogate marker for the activity of centrally acting AChE inhibitors (AChEIs) in the treatment of Alzheimer disease. As a valid peripheral surrogate marker, RBC AChE inhibition should reflect the central pharmacodynamic activity of the compound and should demonstrate a relation with cognitive or global improvement in patients with Alzheimer disease. As a useful clin. tool, RBC AChE inhibition should also provide an advantage in dose optimization. However, the application of surrogate markers in research and clin. use is controversial (Prentice, 1989; Gotzsche, 1996; Colburn, 1997; De Gruttola et al., 1997). For instance, surrogate markers that have been identified or applied inappropriately can lead to erroneous conclusions, slowing the drug development process (Colburn, 1997). Also, the validation of surrogate markers for the pharmacodynamic activity of central nervous system drugs is not always possible because samples of brain tissue cannot be analyzed in humans. Finally, although validation of peripheral markers for central nervous system drugs has been approached via anal. of cerebrospinal fluid (Cutler et al., 1998a), few markers have been subjected to such rigorous evaluation in clin. studies. The extent to which measures of peripheral AChE inhibition accurately model central drug activity and therapeutic effectiveness of AChEIs, both as individual agents and as a drug class, is the focus of this review. AChEIs comprise a group of structurally diverse compds. with a wide range of relative specificities for the various mol. species of cholinesterase found in plasma, RBCs, and the brain. Studies of RBC AChE inhibition after administration of AChEIs in animals are of limited utility because of the differential sensitivity of AChEIs for human vs. animal forms of AChE, the poor correlation between EDs in animals and humans, and the lack of

standardized measurements of effectiveness. Although clin. studies of donepezil, metrifonate, and eptastigmine have suggested the potential use of RBC AChE inhibition as a predictor of clin. response, the degree of inhibition yielding maximum cognitive improvements was highly variable from compound to compound (30-80%). Further, investigators did not prove a relation between central and peripheral pharmacodynamics or demonstrate an advantage over dose in the ability of RBC AChE inhibition to predict clin. response. A study of rivastigmine in patients with Alzheimer disease revealed that cerebrospinal fluid AChE inhibition correlated well with cognitive performance, whereas peripheral inhibition did not. Therefore, RBC cholinesterase inhibition is not a reliable surrogate marker for the activity of AChEIs as a class of drugs, and its usefulness as a dose optimization tool for individual agents has yet to be demonstrated clearly.

IT 123441-03-2, Rivastigmine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RBC cholinesterase inhibition, a useful surrogate marker for cholinesterase inhibitor activity in alzheimer disease therapy i)

RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:640694 CAPLUS
DN 131:276965
TI Therapeutic system which can be moisture activated
IN Bracht, Stefan
PA LTS Lohmann Therapie-Systeme G.m.b.H., Germany
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9949853 | A1 | 19991007 | WO 1999-EP1802 | 19990318 |
| W: AU, CA, JP, KR, MX, NO, SI, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| DE 19814087 | A1 | 19991014 | DE 1998-19814087 | 19980330 |
| CA 2326662 | A1 | 19991007 | CA 1999-2326662 | 19990318 |
| CA 2326662 | C | 20070116 | | |
| AU 9933312 | A | 19991018 | AU 1999-33312 | 19990318 |
| EP 1069892 | A1 | 20010124 | EP 1999-914523 | 19990318 |
| EP 1069892 | B1 | 20020807 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI | | | | |
| JP 2002509879 | T | 20020402 | JP 2000-540819 | 19990318 |
| AT 221774 | T | 20020815 | AT 1999-914523 | 19990318 |

| | | | | | |
|---|---|---|---|---|---|
| | PT 1069892 | T | 20021231 | PT 1999-914523 | 19990318 |
| | ES 2182507 | T3 | 20030301 | ES 1999-914523 | 19990318 |
| | NO 2000004835 | A | 20000926 | NO 2000-4835 | 20000926 |
| | MX 2000PA09579 | A | 20020311 | MX 2000-PA9579 | 20000929 |
| | US 7175853 | B1 | 20070213 | US 2000-647289 | 20001115 |
| PRAI | DE 1998-19814087 | A | 19980330 | | |
| | WO 1999-EP1802 | W | 19990318 | | |

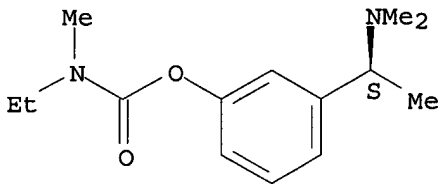
AB A therapeutic system is provided for the temporal and controllable administration of ≥1 therapeutically active substance to a human or animal by diffusion through the skin or a mucous membrane. The active substance is initially available in a 1st state (specifically, as a salt) for production and storage; in this state, the active substance is chemical stable and is insufficiently permeable for the skin or a mucous membrane. The active substance is transformed into a 2nd state (an acid or base) at the application site when exposed to moisture; in this state, the active substance can diffuse through the skin or a mucous membrane, and is absorbed into the organism. Transformation of the salt into an acid or base by exposure to water is facilitated by an active agent also contained in the system; this active agent is a solid which reacts in aqueous solution in an acidic or basic manner or is a mixture of such substances. This active agent contains ≥5% bound or entrapped water. Thus, the anti-Alzheimer's drug ENA 713 H tartrate 10 and Na2SiO3.5H2O 3 were mixed with a solution of silicone adhesive Bio-PSA Q7-4301 in C6H6. The resulting dispersion was spread on a PET film coated with a dehesive fluoropolymer to a surface d. of 60 g/m2 after drying, and laminated with Hostaphen RN film. This laminate released .apprx.15 μg ENA 713/cm2/24 h in permeation expts. with bovine udder skin. compared to .apprx.5 μg/cm2 for similar prepns. containing anhydrous Na2SiO3 or no activator.

IT 123441-03-2, ENA 713 free base
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conversion to free base; therapeutic system which can be moisture activated)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




IT 129101-54-8, ENA 713
RL: RCT (Reactant); RACT (Reactant or reagent)
(therapeutic system which can be moisture activated)

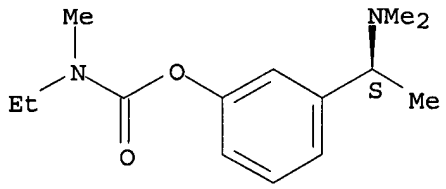
RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2
CMF C14 H22 N2 O2

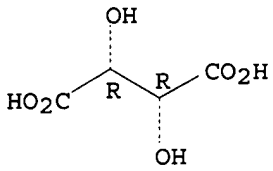
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

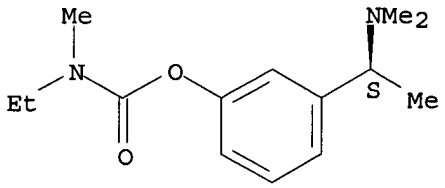
L10 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:601548 CAPLUS
DN 130:55
TI Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease
AU Polinsky, Ronald J.
CS Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
SO Clinical Therapeutics (1998), 20(4), 634-647
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica
DT Journal; General Review
LA English
AB A review with 25 refs. Rivastigmine (ENA 713, or carbamoylatine) is an acetylcholinesterase (AChE) inhibitor with brain-region selectivity and a long duration of action. Both preclin. studies and studies in human volunteers have shown that rivastigmine induces substantially greater inhibition of AChE in the central nervous system (CNS) compartment than in the periphery (40% inhibition of central AChE compared with 10% inhibition of plasma butylcholinesterase in healthy volunteers). Moreover, rivastigmine preferentially inhibits the G1 enzymic form of AChE, which predominates in the brains of patients with Alzheimer's disease (AD). Evidence from animal studies also suggests that rivastigmine is a more potent inhibitor of AChE in the cortex and hippocampus, the brain regions most affected by AD. Absorption of rivastigmine is rapid and almost complete (>96% of the administered dose). Extensive, saturable first-pass metabolism, however, leads to bioavailability of approx. 35% of the administered dose and nonlinear pharmacokinetics. The principal metabolite of rivastigmine has at least 10-fold lower activity against AChE compared with the parent drug. Rivastigmine is completely metabolized; the major route of elimination of the metabolites is renal. Although patients with AD demonstrate 30% to 50% higher plasma concns. of rivastigmine and its principal metabolite than do healthy elderly patients, there is no evidence of drug accumulation, which is consistent with rivastigmine's short pharmacokinetic half-life. Distribution of rivastigmine into the CNS is extensive, and inhibition of AChE in the cerebrospinal fluid is detectable 1.2 h after oral dosing in both healthy

volunteers and patients with AD. Peak activity is reached somewhat more slowly in AD patients than in healthy subjects, and the inhibitory effects have a longer duration (6.0 vs. 2.4 h and 12.0 vs. 8.5 h, resp.). Rivastigmine is inactivated during the process of interacting with and inhibiting AChE, and, in contrast to other AChE inhibitors, the hepatic cytochrome P 450 (CYP-450) system is not involved in the metabolism of rivastigmine. This reduces its propensity to interact with drugs metabolized by specific CYP-450 isoenzymes. Consistent with rivastigmine's pharmacokinetic and pharmacodynamic profiles, Phase II and III trials have demonstrated that the drug is a well-tolerated and effective treatment for AD.

IT 123441-03-2, Rivastigmine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. pharmacol. of rivastigmine, a new-generation acetylcholinesterase inhibitor for treatment of Alzheimer's disease, in humans and laboratory animals)

RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s rivastigmine
L11 620 RIVASTIGMINE

=> s hydrogentartrate
L12 52 HYDROGENTARTRATE

=> s L11 and L12
L13 6 L11 AND L12

=> d L13 1-6 bib abs hitstr

L13 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:313129 CAPLUS
TI Synthesis of S-(+)-rivastigmine hydrogentartrate
AU Feng, Jin; Chen, Wei-min; Sun, Ping-hua
CS Dep. Med. Chem., Sch. Pharmacy, Jinan Univ., Guangzhou, 510632, Peop. Rep. China
SO Nanfang Yike Daxue Xuebao (2007), 27(2), 177-180
CODEN: NYDXAN; ISSN: 1673-4254
PB Nanfang Yike Daxue Xuebao Bianjibu
DT Journal
LA Chinese
AB Objective: To optimize the synthetic procedure of S-(+)-rivastigmine hydrogentartrate which was known as an agent for the treatment of Alzheimer disease. Methods: S-(+)-rivastigmine hydrogentartrate was synthesized by using 1- (3-hydroxyphenyl)ethanone as the starting material via oximation, reduction and N-methylation to produce the key intermediate 3-1-dimethylaminoethylphenol, which finally reacted with N-ethyl-N-methylcarbamoyl chloride. The enantiomers were resolved with

di(+)-p-toluoyl-D-tartaric acid, and the title compound was prepared by mixing S-rivastigmine base with L-(+)-tartrate. Results: The total yield of S-(+)-rivastigmine hydrogentartrate was 4.17%. Conclusion: The materials in this procedure are all com. available. The reaction conditions are mild and total yield is high.

L13 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:561746 CAPLUS
DN 143:77963
TI Process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate
IN Gaitonde, Abhay; Mangle, Mangesh
PA Generics UK Limited, UK
SO Brit. UK Pat. Appl., 13 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI GB 2409453 | A | 20050629 | GB 2003-29970 | 20031224 |
| WO 2005061446 | A2 | 20050707 | WO 2004-GB50042 | 20041217 |
| WO 2005061446 | A3 | 20060105 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| EP 1697313 | A2 | 20060906 | EP 2004-806260 | 20041217 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS

PRAI GB 2003-29970 A 20031224
WO 2004-GB50042 W 20041217
OS CASREACT 143:77963; MARPAT 143:77963
AB Rivastigmine hydrogentartrate is prepared from 3-hydroxyacetophenone in a process which has the advantage of avoiding the preparation of zwitterionic intermediates which are very water soluble and need to be isolated by concentration of aqueous solvent; this process is therefore suited to the industrial-scale manufacture of aminoalkylphenyl carbamates. The large amts. of sulfated ash residues left in the product when prepared by prior-art processes and the use of pyrophoric and reagents such as sodium hydride may be avoided by using the title method.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:300512 CAPLUS
DN 134:305320
TI Rivastigmine for the treatment of ocular disorders
IN Goldblum, David
PA Novartis Ag, Switz.; Novartis-Erfindungen
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
| PI | WO 2001028553 | A1 | 20010426 | WO 2000-EP10234 | 20001017 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 6534541 | B1 | 20030318 | US 2000-686025 | 20001011 |
| | CA 2384690 | A1 | 20010426 | CA 2000-2384690 | 20001017 |
| | EP 1225890 | A1 | 20020731 | EP 2000-992430 | 20001017 |
| | EP 1225890 | B1 | 20041229 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| | JP 2003512324 | T | 20030402 | JP 2001-531383 | 20001017 |
| | AU 766001 | B2 | 20031009 | AU 2001-28349 | 20001017 |
| | NZ 518164 | A | 20031031 | NZ 2000-518164 | 20001017 |
| | AT 285764 | T | 20050115 | AT 2000-992430 | 20001017 |
| | PT 1225890 | T | 20050531 | PT 2000-992430 | 20001017 |
| | ES 2234708 | T3 | 20050701 | ES 2000-992430 | 20001017 |
| | US 2003119832 | A1 | 20030626 | US 2003-349718 | 20030123 |
| | US 6835748 | B2 | 20041228 | | |
| PRAI | EP 1999-120678 | A | 19991019 | | |
| | US 2000-686025 | A3 | 20001011 | | |
| | WO 2000-EP10234 | W | 20001017 | | |

OS MARPAT 134:305320

AB The present invention is in particular related to the use of rivastigmine in the manufacture of a medicament for the treatment of ocular disorders selected from glaucoma, normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2001:247162 CAPLUS

DN 134:271266

TI Oral controlled release formulations containing rivastigmine

IN Shah, Rajen; Khanna, Satish Chandra; Kalb, Oskar; Ogorka, Joerg

PA Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.

SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| | | | | | |
|---|---|---|---|---|---|
| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
| PI | WO 2001022944 | A1 | 20010405 | WO 2000-EP9455 | 20000927 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2379595 | A1 | 20010405 | CA 2000-2379595 | 20000927 |
| | BR 2000014440 | A | 20020618 | BR 2000-14440 | 20000927 |
| | EP 1216032 | A1 | 20020626 | EP 2000-971290 | 20000927 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| | TR 200200683 | T2 | 20020722 | TR 2002-683 | 20000927 |

| | | | | | |
|---|---|---|---|---|---|
| | HU 2002002744 | A2 | 20030128 | HU 2002-2744 | 20000927 |
| | JP 2003510268 | T | 20030318 | JP 2001-526156 | 20000927 |
| | NZ 517335 | A | 20031031 | NZ 2000-517335 | 20000927 |
| | AU 769646 | B2 | 20040129 | AU 2001-10197 | 20000927 |
| | RU 2281758 | C2 | 20060820 | RU 2002-109236 | 20000927 |
| | NO 2002001452 | A | 20020322 | NO 2002-1452 | 20020322 |
| | ZA 2002002369 | A | 20021028 | ZA 2002-2369 | 20020325 |
| | US 2006246101 | A1 | 20061102 | US 2006-479020 | 20060630 |
| PRAI | GB 1999-23045 | A | 19990929 | | |
| | WO 2000-EP9455 | W | 20000927 | | |
| | US 2002-89265 | B1 | 20020327 | | |

AB Oral controlled release pharmaceutical compns. capable of releasing a therapeutically ED of a drug, e.g., rivastigmine, are described. Thus, tablets contained rivastigmine hydrogen tartrate 7.2, microcryst cellulose fine powder 25.95, HPMC K100M 18.75, microcryst cellulose granular powder 22.35, Mg stearate 0.375, and highly dispersed SiO2 0.375 mg.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:127379 CAPLUS
DN 132:274211
TI Inhibitory effect of orally administered donepezil hydrochloride (E2020), a novel treatment for Alzheimer's disease, on cholinesterase activity in rats
AU Kosasa, T.; Kuriya, Y.; Matsui, K.; Yamanishi, Y.
CS Tsukuba Research Laboratories, Eisai, Tsukuba, Ibaraki, Japan
SO European Journal of Pharmacology (2000), 389(2/3), 173-179
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB Donepezil hydrochloride ((±)-2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-indan-1-one monohydrochloride: E2020: donepezil) is a potent and selective acetylcholinesterase inhibitor developed for the treatment of Alzheimer's disease. The present expts. were designed to compare the inhibitory effects of orally administered donepezil and other cholinesterase inhibitors, tacrine (9-amino-1,2,3,4-tetrahydroacridine hydrochloride), (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenylcarbamate hydrogentartrate (ENA-713, rivastigmine ) and 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone fumarate (TAK-147), on the cholinesterase activity in the brain and plasma of rats. Moreover, in order to validate the cholinesterase inhibition data, we measured the brain and plasma concns. of these drugs. Oral administration of donepezil, tacrine, ENA-713 or TAK-147, caused a dose-dependent inhibition of brain and plasma cholinesterase activities. The ID50 values of these compds. for brain cholinesterase activity were 6.3, 40.5, 7.2 and 26.8 μmol/kg, resp. On the other hand, the ID50170, 9.7 and 51.2 μmol/kg, resp. Thus, the ratios of the ID504.2, 1.3 and 1.9, resp. Brain and plasma concns. of donepezil, tacrine and TAK-147 increased dose-dependently. The ratios of the concns. (brain/plasma) of these compds. were 6.1-8.4 for donepezil, 14.5-54.6 for tacrine and 7.0-20.6 for TAK-147. The values of 50% inhibitory concentration of these drugs in the brain were 0.42, 3.5 and 1.1 nmol/g, resp. In contrast, the brain and plasma concns. of ENA-713 at all doses, except the two highest doses, were below the quantification limit. These results suggest that orally administered donepezil satisfactorily penetrates into the brain and inhibits cholinesterase there, and that donepezil is a potent and selective inhibitor of brain cholinesterase in comparison with plasma cholinesterase in vivo.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1999:693076 CAPLUS
DN 131:332022
TI Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular acetylcholine in the hippocampus of rats
AU Kosasa, Takashi; Kuriya, Yuka; Matsui, Kenji; Yamanishi, Yoshiharu
CS Tsukuba Research Laboratories, Tsukuba, 300-2635, Japan
SO European Journal of Pharmacology (1999), 380(2/3), 101-107
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The effects of oral centrally acting acetylcholine esterase (AChE) inhibitors donepezil HCl, tacrine HCl, and ENA-713 (rivastigmine hydrogentartrate) developed for the treatment of Alzheimer disease on the extracellular acetylcholine concns. in the brain hippocampus of rats were evaluated using microdialysis without adding cholinesterase inhibitors to the perfusion solution We also compared the inhibition of brain AChE and brain concns. of the 3 drugs. Donepezil at 2.5 mg/kg and tacrine at 5 mg/kg had significant effects for >6 h. At these doses, the maximum increases were 499 and 422% of the pretreatment levels and were observed at .apprx.1.5 and .apprx.2 h after administration of donepezil and tacrine, resp. ENA-713 had significant effects at 0.625, 1.25, and 2.5 mg/kg, which lasted for about 1, 2, and 4 h, resp. The maximum increases produced by these doses at .apprx.0.5 h after administration were 190, 346, and 458% of the pretreatment levels, resp. The time courses of brain AChE inhibition with 2.5 mg donepezil/kg, 10 mg tacrine/kg, and 2.5 mg ENA-713/kg were mirror images of the extracellular acetylcholine-increasing action at the same doses. The time courses of brain concns. of the drugs after oral administration of 2.5 mg donepezil/kg and 10 mg tacrine/kg were consistent with the course of brain AChE inhibition at the same doses; there was a linear relation between these parameters. Brain concns. of ENA-713 given at 2.5 mg/kg was below the limit of quantification at all time points measured. Thus, oral administration of donepezil, tacrine, and ENA-713 increases acetylcholine concns. in the synaptic cleft of the brain hippocampus mostly through AChE inhibition. Donepezil has a more potent activity than tacrine and a longer-lasting effect than ENA-713 on the central cholinergic system.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 209.03 | 381.34 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -31.20 | -31.20 |

STN INTERNATIONAL LOGOFF AT 08:36:38 ON 14 DEC 2007